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All living systems have evolved on planet Earth in the presence of gravity. Every blade of grass grows in its particular way and every cell divides the way it does, influenced by gravity. The hypothalamic-pituitary-adrenal system is no exception. However, all our knowledge of this system has been obtained in the presence of one relatively constant environmental factor--gravity. We can only hypothesize about the role gravity has played in the evolution of living systems. Would degenerative changes in gravity receptors specifically, and neuronal organization in general, result during short or long exposures to the absence of gravity or microgravity? How would such changes affect the function of the hypothalamic-pituitary adrenal system?

In the early 1960s, advances in World War II developed technology, coupled with man's hunger for exploration, made it possible, through spaceflight, to leave the Earth's gravitational forces and become virtually weightless. Eminent scientists of the time predicted dire consequences. Among the life-threatening predictions were the inability to swallow or void. Other predictions were based on clinical experience with polio victims and paraplegics and of controlled studies in healthy volunteers (Sandler and Vernikos, 1986), of the effects of inactivity on bone and muscle, since weightlessness removes the load and resistance associated with normal musculoskeletal activity on Earth. The controlled studies by Dietrick, Whedon and Shorr (1948) of immobilization of four healthy young men in body casts, demonstrated clearly what was beginning to be recognized in the clinical setting, that inactivity in healthy individuals would, at the very least, lead to substantial changes in calcium, phosphorus, and nitrogen.

Pituitary-adrenal and sympathetic responses to stress were among the first to be considered likely and they were indeed measured before and after the very first Mercury flights which lasted from only 15 min to some hours (Leach, 1971). To tease out the effects of weightlessness and thereby gravity is not a simple matter. Conditions associated with early spaceflight included high-gravity accelerations during liftoff and reentry, breathing 100% oxygen at 5 psi, being essentially immobilized in a spacesuit, in cramped quarters for days, in addition to physical dangers and emotional unknowns as well as the excitement of the whole event. In addition, extravehicular activity and landing on the moon should also have contributed to the measured effects. With the advent of the Space Shuttle many of these variables (but not all) have been removed so that we may be coming closer to determining what weightlessness really does.

As in any field study, the practical problems of obtaining in-flight samples, as well as the need to minimize interference with the crew's heavy work schedule, are an additional impediment to obtaining the best data. Much of the data, at least on blood and urine samples, have relied on pre- and postflight collections (Fischer et al., 1967; Leach et al., 1970) when the relative contribution of reentry to the response must be taken into account. Similarly, in most animal flight experiments, particularly those flown on the COSMOS series of Soviet biological satellites, investigators have relied on pre- and postflight data to extrapolate to what might have been happening in flight (Souza, 1979). For some systems, that may indeed be valid (Morey and Baylink, 1978; Wronski and Morey, 1983), but for a system as dynamic as the pituitary-adrenal this would not be expected to hold true particularly after flights of relatively short duration when adaptation to a new steady state may not be expected to have been reached.

Gemini VII with two astronauts on board, which orbited the Earth for 14 days in December of 1965, was the first flight on which samples of any kind (in this case urine samples) were collected and stored in flight for postflight analysis. It was the first effort to carry out a detailed metabolic study, and as part of that effort, Harry Lipscomb carried out the endocrine components of that study (Lutwak et al., 1969). Figure 1 shows the urinary excretion of 17-Hydroxycorticosteroids (17-OHCS) in the two astronauts, before, during and after the 14-day orbital spaceflight. In both indivuduals 17-OHCS excretion was decreased throughout the flight, but there was an increase on the day of splashdown and plasma 17-OHCS were also high immediately postflight. Similarly, throughout the Apollo series of missions to the moon, that followed Gemini, whenever measurements in flight were possible, 17-OHCS excretion was also reduced whereas cortisol excretion was normal or increased (Leach et al., 1975). Plasma cortisol and ACTH data obtained on recovery showed no evidence that they increased (Leach et al., 1972), possibly because recovery sampling occurred at a different time point in the diurnal cycle (Leach and Campbell, 1971).

As we moved into the Skylab era, a great opportunity to obtain in-flight information on the adaptive responses to more prolonged exposures to weightlessness presented itself. There were three Skylab missions of 28, 56, and 82 days. As in Gemini VII dietary composition and intake was controlled. Early morning blood samples were drawn at intervals throughout each mission, and 24-hr urine samples were collected and stored for postflight analysis. Cortisol excretion was extremely high for the first 4 days of the mission in all crew members. It then decreased, but remained elevated above preflight control levels (Leach, 1977, 1981). Plasma cortisol levels were also increased during these flights, paralleling the changes in cortisol excretion. It should be pointed out that Skylab differed from previous spacecraft by being considerably larger; the environment was no longer hyper-oxic and hypobaric so that space suits did not need to be worn. However, greater mobility brought on more severe symptoms of space motion sickness and that probably accounts to a great extent for the increased cortisol levels during the first few days of flight. In addition, the vigorous exercise throughout the flight designed to reduce cardiovascular and musculoskeletal deconditioning may have further contributed to the sustained higher adrenal activity. Perhaps as a result of this, plasma ACTH was generally reduced, particularly toward the end of the 84-day mission.

The advent of the Space Shuttle brought with it milder launch and landing conditions and some greater degree of comfort to living in space. Spacelab 1, 2, and 3 once more provided the possibility of obtaining some in-flight data. However, missions were of relatively short duration (4-7 days) so that only the initial phases of the adaptive response to spaceflight could be studied. Data from Spacelab provided results that differed once again from those of Skylab (Figure 2) (Leach et al., 1985; Leach et al., 1987). Plasma ACTH increased during flight in Spacelab whereas it had decreased in Skylab; plasma cortisol decreased in Spacelab, but had remained elevated throughout the Skylab missions. The reasons for these differences are not immediately obvious, but it appears likely that apart from the initial bout of Space Adaptation Syndrome (nausea and occasional vomiting in 70% of crewmembers), Spacelab conditions were not as stressful as in the Skylab missions, though the numerous and uncontrollable variables of each mission make interpretation of these data rather difficult. However, some uncoupling of normal pituitary-adrenal relationships have been observed.

One way to unravel the contribution of such variables to the observed effects is to identify a suitable simulation model and thereby isolate if possible the effects of simulated weightlessness on the system. It is evident that it is not possible to be weightless on the Earth's surface with the exception of brief periods that can be achieved during parabolic flight. Simulation models have relied then on mimicking some of the known physiological responses to weightlessness such as inactivity or the headward shift of body fluids using immersion in water or bedrest, in particular head-down or antiorthostatic bedrest. Since immersion does not lend itself to prolonged exposures, -6° head down bedrest has become the simulation model of choice.

In a series of several bedrest studies we have used healthy male and female volunteers, aged 30-50, to match the age of the astronaut population. Diet and activities have been strictly controlled as are light-dark cycles.

During 7 days of head-down bedrest in eight male and eight female subjects (Dallman et al., 1983; Vernikos, Dallman, Keil and Convertino, unpublished observations) the relationship of early-morning concentrations of plasma cortisol to ACTH was remarkably normal. Cortisol excretion was increased on the first and last day of bedrest in males and was also maintained somewhat above the pre-bedrest control throughout the bedrest period. No such response was evident in females, where in fact there was a tendency for 24-hr cortisol excretion to decrease. Differences between 24-hr excreted cortisol changes and early-morning plasma cortisol levels measured, could have been due to effects of bedrest on binding, metabolism or clearance, or could have reflected altered circadian patterns.

In another 14-day bedrest study with 12 females, 8 a.m. and 8 p.m. plasma cortisol levels showed a progressively decreasing amplitude and mean daily circulating level during the course of the study (Vernikos-Danellis et al., 1978). A similar pattern, however, was seen in the confined ambulatory control subjects, suggesting that the confinement inevitably associated with the bedrest situation may have contributed to this effect. The pattern of 24-hr cortisol excretion in these same female subjects at bedrest for 14 days was similar to that seen in the 7-day study described previously and again was no different from ambulatory controls. At no time have we seen increased cortisol excretion during bedrest in females. The data suggest that the increased cortisol excretion during short-term bedrest in men of this age and in previously reported longer bedrest studies with even younger men (Cardus et al., 1965) was associated with the extent to which individuals perceived bedrest as a stressful situation.

In another group of five 30-50 year old males, head-down bedrest for 30 days also resulted in decreasing cortisol excretion after an initial 12- to 14-day period when cortisol excretion was normal (Vernikos-Danellis, 1988). At the same time, early-morning plasma cortisol concentrations were significantly increased.

While these adaptive adjustments in basal function of the system are taking place, adrenocortical responsiveness to infused ACTH remained unchanged after 6 days of head-down bedrest (Dallman et al., 1984). However, the pituitary-adrenal response to standing was significantly greater than it was prebedrest (unpublished observations). Similarly, after 14 days of bedrest, the responsiveness of the pituitary to another orthostatic stress, that of centrifugation at +3 G_z, was also enhanced (Figure 3). In this case the enhanced responsiveness to centrifugation was probably due to bedrest since the ambulatory, but confined controls showed no such effect. No enhancement of the cortisol response to centrifugation was measurable ($p < 0.05$) providing some indirect evidence that after 14 days of bedrest adrenal sensitivity to

ACTH may be reduced. The further evidence of the instability of the system was obtained during a 56-day horizontal bedrest study, using male subjects (Vernikos-Danellis et al., 1974; Leach et al., 1974). Plasma samples were drawn every 4 hr for 48-hr periods, before, during, and after the end of the 56 days of bedrest. Marked fluctuations were evident in the amplitude and daily mean of the plasma cortisol dirunal rhythm, but overall rhythmicity was maintained, with peak plasma cortisol levels occurring generally at 0800 hr. The rhythm in plasma ACTH, however, showed great instability, and increased in amplitude as bedrest progressed. Figure 4 shows the changes in the 8 a.m. plasma ACTH and cortisol in these subjects where the uncoupling between ACTH and cortisol is more evident, but only after 42 days of bedrest. The increase in ACTH, and the concurrent decrease in plasma cortisol, in the presence of a reasonably synchronized cortisol rhythm, suggests that the primary site of uncoupling involves the negative feedback loop. Changes in adrenal sensitivity to ACTH are not precluded. This is consistent with observations of decreased adrenal sensitivity to ACTH in permanently inactive individuals (Kaplan et al., 1966; Vallbona et al., 1966) in debilitated individuals or in hospitalized, convalescing nonendrocrine patients (Cooke et al., 1964). Alternately, the apparent increase in circulating immunoreactive ACTH may reflect changes in nonbioactive ACTH-like peptides or precursors (Rees, 1988). Similar uncoupling has been observed both in flight and in bedrest studies for the renin-angiotensin-aldosterone system (Dallman et al., 1984; Leach et al., 1985) and the glucose-insulin system (Vernikos-Danellis et al., 1976).

In the presence of Earth's gravity, the return to equilibrium in response to a perturbation takes its course and is predictable. It would appear that in the process of adapting and attaining a new equilibrium in the absence of gravity or of the directional forces of gravity, the hypothalamo-pituitary-adrenal system becomes unstable and decoupled.

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FIGURE CAPTIONS

Figure 1. Twenty-four hour 17-OHCS excretion in the two astronauts before, during, and following the flight of Gemini VII (reprinted with permission from Lutwak et al., 1969).

Figure 2. Mean percent changes in plasma hormones measured in flight and postflight in crewmembers. Bars represent standard error of the mean (reprinted with permission from Leach et al., 1987).

Figure 3. Plasma ACTH and cortisol responses to +3 G_z acceleration in normal female subjects before and after 14 days of bedrest or confinement.

Figure 4. Plasma cortisol and ACTH changes during 56 days of bedrest in healthy males; vertical lines represent standard error of the mean (N = 12).

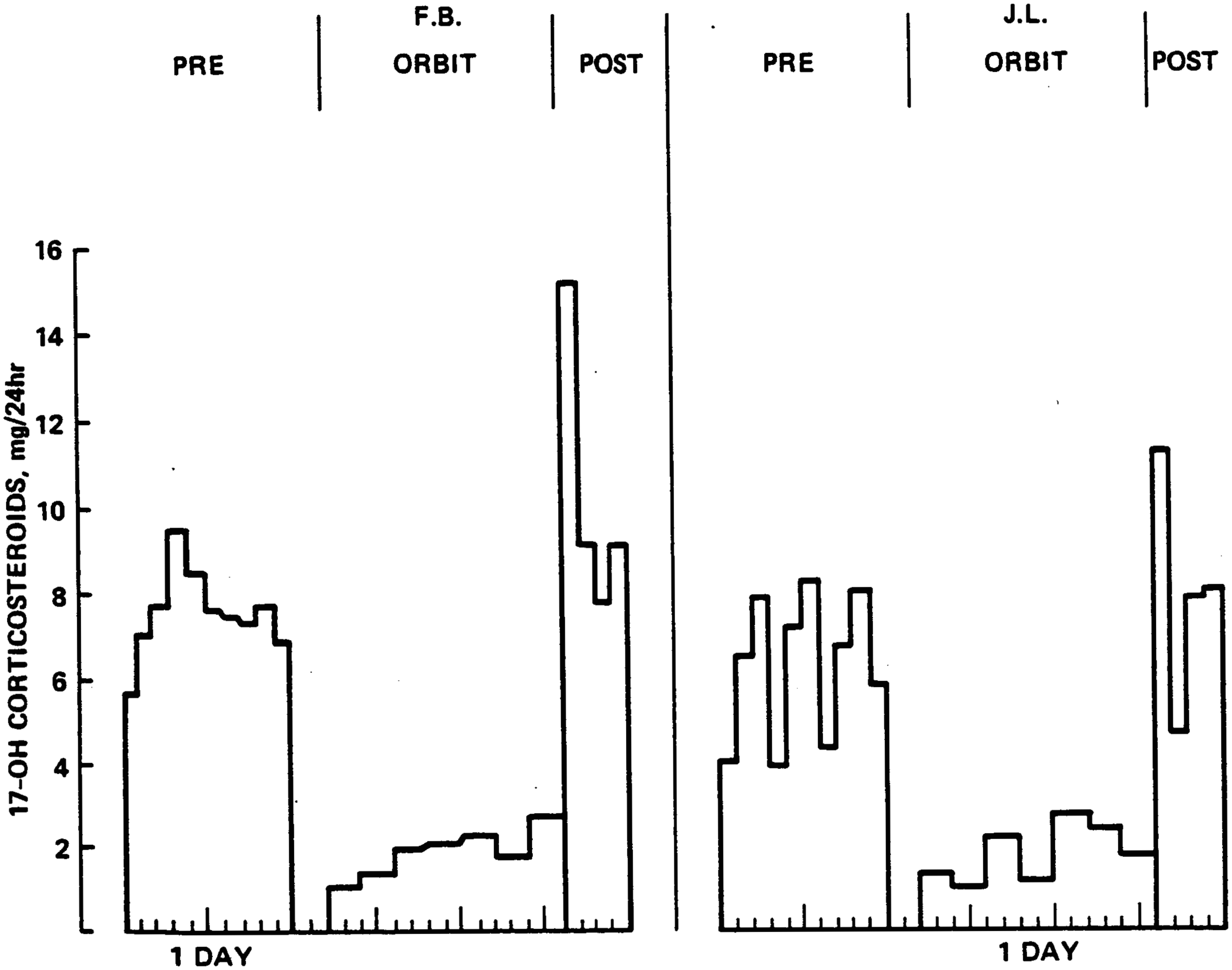
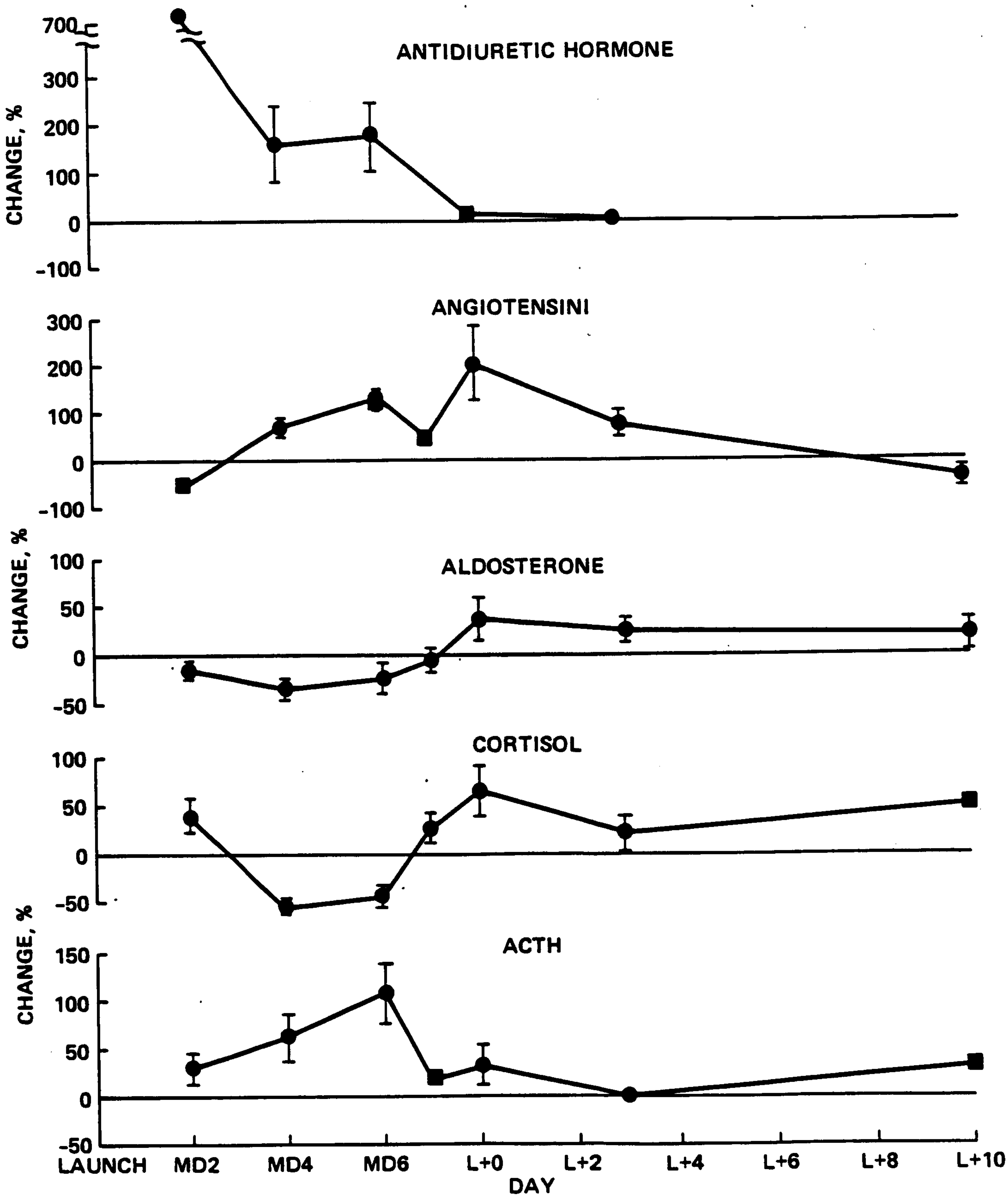
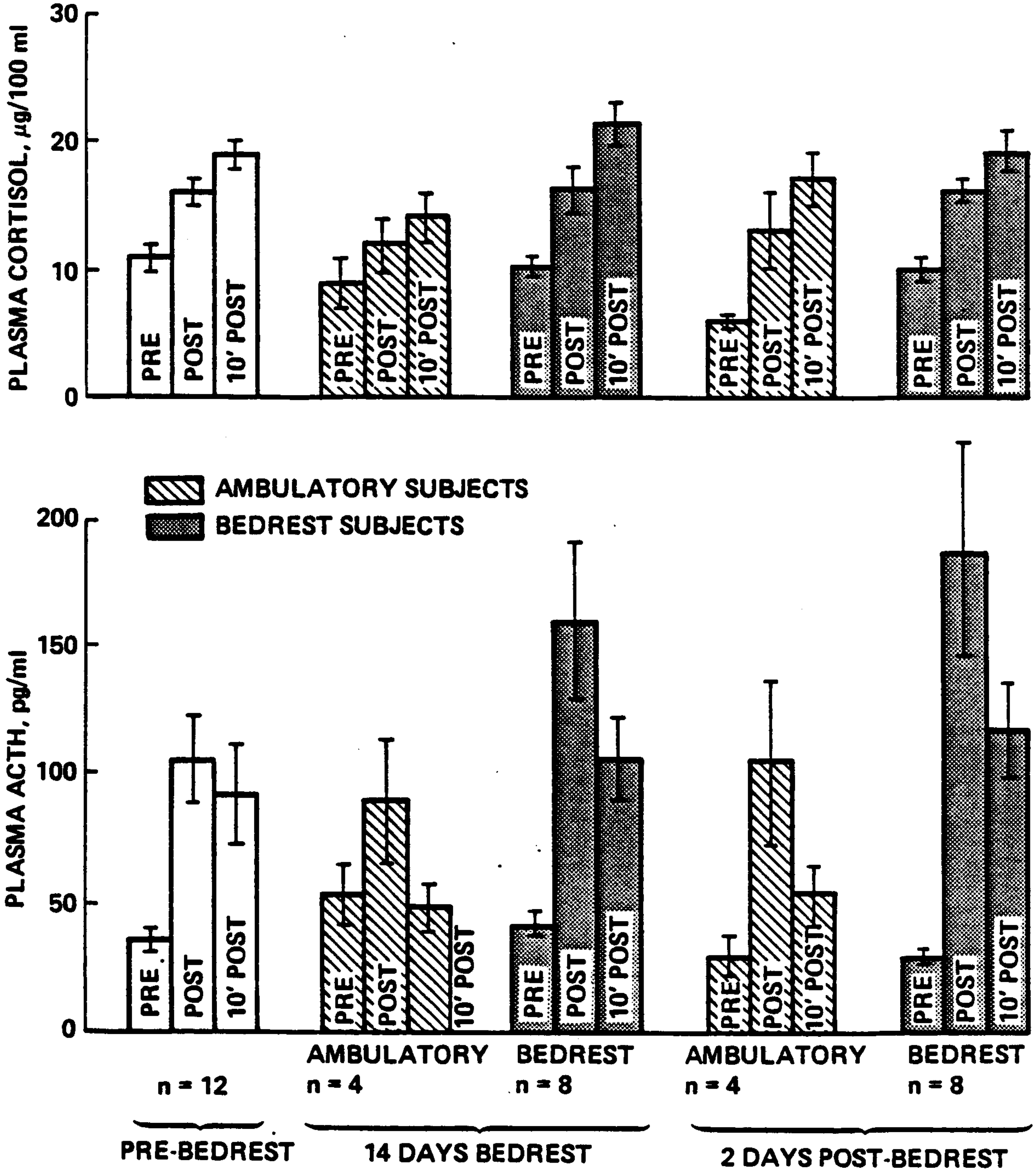

F.B.
PRE
ORBIT
POST
J.L.
PRE
ORBIT
POST
16
14
12
10
8
6
4
2
17-OH CORTICOSTEROIDS, mg/24hr
1 DAY
1 DAY

Fig. 1



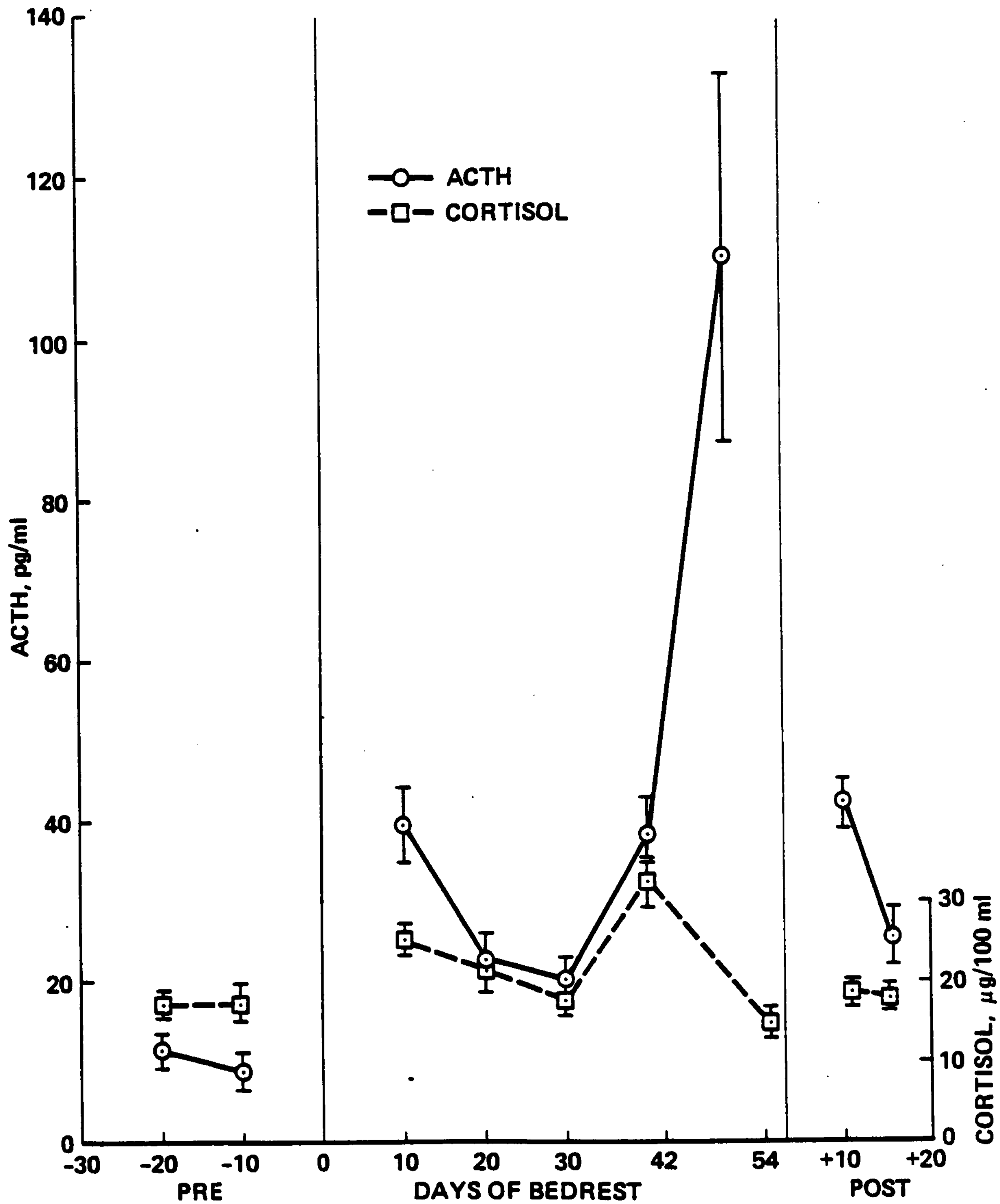
ANTIDIURETIC HORMONE
700
300
200
100
0
-100
CHANGE, %
ANGIOTENSINI
300
200
100
0
-100
CHANGE, %
ALDOSTERONE
100
50
0
-50
CORTISOL
100
50
0
-50
CHANGE, %
ACTH
150
100
50
0
-50
LAUNCH
MD2
MD4
MD6
L+0
L+2
L+4
L+6
L+8
L+10
DAY

Fig. 2



PLASMA CORTISOL, µg/100 ml
30
20
10
0
PRE
POST
10' POST
AMBULATORY SUBJECTS
BEDREST SUBJECTS
PLASMA ACTH, pg/ml
200
150
100
50
AMBULATORY
BEDREST
n = 12
n = 4
n = 8
PRE-BEDREST
14 DAYS BEDREST
2 DAYS POST-BEDREST

Fig. 3



ACTH
CORTISOL
ACTH, pg/ml
CORTISOL, μg/100 ml
140
120
100
80
60
40
20
0
30
20
10
0
-30
-20
-10
0
10
20
30
42
54
+10
+20
PRE
DAYS OF BEDREST
POST

Fig. 4

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16. Abstract

Evidence has been accumulating from spaceflight and ground-simulation studies suggesting that the normal relationship between neuroendocrine driving mechanisms and their respective target organs may become uncoupled; and that the sensitivity of the various components of the closed-loop systems may be altered.

Changes in the regulation of the pituitary-adrenal system and the angiotensinaldosterone system will be discussed in support of this thesis.

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